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EXAMINER	
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ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17-30 and 40-47* is/are pending in the application.

4a) Of the above claim(s) *1-11,22-30 and 40-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14,17-21,46 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

As mentioned in the last office action, the restriction was based on the claims filed on October 17, 2005 (Article 34 claims) and not the amended claims of February 4, 2008. Therefore, the amendments of February 4, 2008 will not be considered for purposes of this discussion.

The technical feature shared among the inventions listed as Groups I-IV,VII and VIII is a polypeptide (or nucleic acid encoding the polypeptide) comprising a protein of interest and a large envelope polypeptide. Even though the polypeptide can be used in a VLP, the claims of Group II are only drawn to the polypeptide, not VLPs containing the polypeptide or methods of using the VLPs. The noted shared technical feature (i.e., a polypeptide (or nucleic acid encoding the polypeptide) comprising a protein of interest and a large envelope polypeptide) does not provide a contribution over the prior art, as evidenced by the teachings of Kuroda et al. (Journal of Biological Chemistry, 1992, 267(3):1953-1961). Kuroda et al. teaches a polypeptide comprising the signal peptide from chicken lysozyme (i.e., protein of interest) and HBV large envelope polypeptide (**Note: claim 1 does not require that the large envelope polypeptide be from an avian HBV**). Further, the shared technical feature, a polypeptide comprising a protein of interest and a large envelope polypeptide, is also disclosed in George et al. (U.S. Patent Application No. 2004/0001853) (see the art rejection below). Hence, in the absence of a contribution over the prior art, the noted shared technical feature is not a shared special technical feature. Without a shared special technical feature, the

inventions listed as Groups I-IV, VII and VIII lack unity with one another. Groups V and VI do not have a technical feature in common with each other or with the inventions of Groups I-IV, VII and VIII. Therefore, the inventions listed as Groups I-VIII lack unity with one another.

Applicants are reminded that they may petition the Office regarding the restriction requirement.

Withdrawn Rejections

The rejection of claims 16-19 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of applicants' cancellation of claim 16 and amendments to the claims.

The rejection of claims 12-14, 16-19 and 21 under 35 U.S.C. 102(e) as being anticipated by George et al. (U.S. Patent Application No. 2004/0001853) as evidenced by Glebe et al. (World J Gastroenterol, 2007, 13(1): 91-103) is withdrawn in view of applicants' amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14, 17-21, 46 and 47are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to, *inter alia*, a fusion polypeptide for use in the assembly of a VLP comprising an avian hepadnavirus small envelope (S) polypeptide or a functional derivative thereof, said fusion polypeptide comprising a polypeptide of interest (POI) and at least a particle-associating portion of a large envelope polypeptide (L) of an avian hepadnavirus, wherein the POI is not a pre-S region of an avian hepadnavirus, wherein the POI is located (i) in the pre-S domain, (ii) N-terminally to the L polypeptide, (iii) at the amino terminal side of the S domain, or (iv) at the amino terminal side of the S domain minus the TM1 domain, and wherein the fusion polypeptide associates with said VLP comprising an avian hepadnavirus S polypeptide or a functional derivative thereof. In addition, the claims are drawn to, *inter alia*, polypeptides that are at least 90% identical to SEQ ID NO:8 or 9.

The written description rejection is made because the claims are interpreted as being drawn to a genus of products recited as functional derivatives of avian large envelope and polypeptides that are at least 90% identical to SEQ ID NO:8 or 9. The applicable standard for the written description requirement can be found in MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Probe Inc., 63 USPQ2d 1609; Vas- Cath Inc. v. Mahurkar, 19 USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004). To provide adequate written description and evidence of

possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are SEQ ID NOs: 8 and 9 and the function of the product being claimed (assembling into VLPs). There is no disclosure of any particular portion of SEQ ID NO:8 or 9 that must be conserved (or changed) to be a functional derivative thereof or a polypeptide that is at least 90% identical to SEQ ID NO: 8 or 9 and maintain the desired function.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The specification discloses at page 23: Functional derivatives of the instant L polypeptide include fragments, parts or portions of the parent molecule which retain the ability of the L polypeptide to associate with the particle formed by S polypeptide, or at least where such ability is not substantially lost.

The specification discloses at page 24: The term "functional derivative" also extends to polypeptides having one or more amino acid mutations or modifications. Mutations may be derived from additions, insertions, deletions or substitutions of amino acids. Substitutions are preferably conservative amino acid substitutions. Modifications may include the addition of flanking sequences which enhance viral particle assembly or stability.

There is no guidance for producing the functional derivative. It is not clear what portions or amino acids of SEQ ID NO: 8 or 9 or avian small envelope that can be changed to produce a functional derivative that still assembles. It is not clear what portions or amino acids of SEQ ID NO: 8 or 9 must be conserved to produce a functional derivative that still assembles. It is also not clear where additions, insertions, deletions or substitutions of amino acids occur within SEQ ID NO: 8 or 9. Applicants have not provided examples of functional derivatives or polypeptides that are at least 90% identical to SEQ ID NO: 8 or 9.

The court clearly states in Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented what is claimed. As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of functional derivatives of avian large envelope and polypeptides that are at least 90% identical to SEQ ID NO: 8 or 9. Given that the specification has only described the structure and function of SEQ ID NOs: 8 and 9, the full breadth of the claims does not meet the written description provision of 35 U.S.C. 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites "medium stringency." It is unclear what is meant by "medium stringency." Page 32 of the specification defines "medium stringency" as encompassing from "at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5 M to at least about 0.9 M salt for hybridization, and at least about 0.5 M to at least about 0.9 M salt for washing conditions." The specification further states that moderate stringency is 2 x SSC buffer, 0.1% w/v SDS at a temperature in the range 20°C to 65°C. The specification does not limit the definition of "medium stringency" to any specific definition or conditions, thus the term "medium" in the context of "stringency" is relative and lacks comparative basis.

Response to Arguments

In the reply dated November 12, 2008, applicants argue that the definition provided in the specification for "medium stringency" is consistent with the understanding of those of skill in the art. This argument has been fully considered, but not found persuasive.

The definition for medium stringency is not specific and does not define the temperature, amount of SSC or amount of SDS. However, moderate stringency is

specifically defined and definite. Applicants may consider amending the claim to recite "moderate stringency."

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-14, 17-19, 21, 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over George et al. (U.S. Patent Application No. 2004/0001853) as evidenced by Glebe et al. (World J Gastroenterol, 2007, 13(1): 91-103).

The claims are drawn to, *inter alia*, a fusion polypeptide for use in the assembly of a VLP comprising an avian hepadnavirus small envelope (S) polypeptide or a functional derivative thereof, said fusion polypeptide comprising a polypeptide of interest

(POI) and at least a particle-associating portion of a large envelope polypeptide (L) of an avian hepadnavirus, wherein the POI is not a pre-S region of an avian hepadnavirus, wherein the POI is located (i) in the pre-S domain, (ii) N-terminally to the L polypeptide, (iii) at the amino terminal side of the S domain, or (iv) at the amino terminal side of the S domain minus the TM1 domain, and wherein the fusion polypeptide associates with said VLP comprising an avian hepadnavirus S polypeptide or a functional derivative thereof.

George et al. discloses fusion constructs comprising DHBV PreS or PreS/S and a protein of interest, the Fc portion of an antibody (see Figure 16 and Example 5, 6 and 31) located C-terminally to the DHBV PreS or PreS/S protein. The full length DHBV protein comprises the small envelope (S) polypeptide and at least a particle-associating portion of a large envelope polypeptide (L) of DHBV. The fusion protein can assemble into VLP because it contains all of the large envelope polypeptide (L), which is also known as preS as evidenced by Glebe et al. (see Figure 2 of Glebe et al.). George et al. also teaches a chimeric antigen comprising an immune response domain and a target binding domain, wherein the immune response domain comprises one or more sequences comprising an HBV core protein, HBV S protein, HBV S1 protein, HBV S2 protein, combinations thereof, and recombinant molecules thereof, and wherein the target binding domain comprises a xenotypic antibody fragment (see, for example, claim 20). Thus, George et al. teaches the use of the S protein in its fusion proteins. George et al. further discloses SEQ ID NOs:43 and 44, which comprise instant SEQ ID NOs:6 and 8 and SEQ ID NOs:7 and 9, respectively.

George et al. does not teach that the protein of interest is located (i) in the pre-S domain, (ii) N-terminally to the L polypeptide, (iii) at the amino terminal side of the S domain, or (iv) at the amino terminal side of the S domain minus the TM1 domain. In addition George et al. does not teach that the particle associating portion comprises the L polypeptide minus the preS domain or minus the TM1 domain, the S domain minus the TM1 domain, or a portion of the L polypeptide which is downstream of TM1 and comprises at least TM2, the 5' cysteine loop between TM1 and TM2, and sequences downstream of TM2. However, it is well within the purview of one of ordinary skill in the fusion protein/vaccine arts to place the protein of interest in various locations such that VLPs still form. Further, using the teachings of George et al. as outlined above, it is well within the purview of one of ordinary skill in the fusion protein/vaccine arts to select various particle associating portions of the L protein (PreS, PreS/S, S, etc.) so long as the desired property is present (i.e., association of fusion proteins such that VLPs form).

With regard to applicants' argument that the fusion proteins of George et al. "most likely" do not form VLPs, applicants have not provided any direct evidence that a fusion protein comprising the entire L protein of DHBV would not form VLPs. The L protein of DHBV contains all the necessary elements to associate and form VLPs. Absent any such evidence, it is reasonable for one of ordinary skill in the art to expect the fusion proteins of George et al. to associate and form VLPs.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over George et al. (U.S. Patent Application No. 2004/0001853) as evidenced by Glebe et al. (World J Gastroenterol, 2007, 13(1): 91-103).

The teachings of George et al. are outlined above. George et al. does not teach that the L polypeptide comprises a signal sequence.

Because many proteins, including chimeric proteins, are expressed in eukaryotic cells, it is also well within the purview of one of ordinary skill in the art to add the appropriate signal sequence to direct the protein through a specific pathway, e.g., the secretory pathway.

Therefore, it would have been obvious to one of ordinary skill in the art to modify the construct taught by George et al. to produce a construct where the protein of interest is located in the L polypeptide and/or the L polypeptide further comprises a signal sequence. One would have been motivated to do so and there would have been a reasonable expectation of success given the fact that such proteins are routinely made in the art. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In the reply dated November 11, 2008, applicants argue that George et al. does not provide any teaching or suggestion of using a signal sequence. This argument has been fully considered, but not found persuasive.

As mentioned above, it would have been obvious to one of ordinary skill in the art to modify the construct taught by George et al. to produce a construct where the L

polypeptide further comprises a signal sequence so that the protein is directed through the secretory pathway and so that the protein is properly glycosylated as needed. One would have been motivated to do so and there would have been a reasonable expectation of success given the fact that such proteins are routinely made in the art. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648